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SPECIFICATION

FOR

PATENT APPLICATION

IN

UNITED STATES OF AMERICA

in the name of JEAN PIERRE KAPLAN
PASCAL GEORGE

assignors to SYNTHELABO

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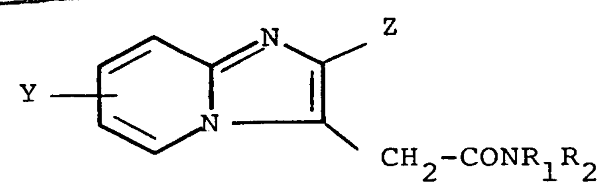
DESCRIPTION

"IMIDAZO [1,2-a] PYRIDINE DERIVATIVES USEFUL IN THERAPY AND THEIR PREPARATION"

The present invention relates to imidazo [1,2-a] pyridine derivatives, useful in therapy and their preparation.

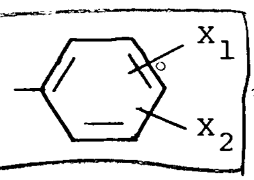
Imidazo [1,2-a] pyridines have already been described in the literature, for example in British Patents 991,589 and 1,076,089 and in various other publications.

The compounds of the present invention have the formula (I)

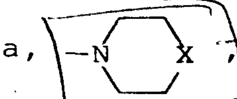


(I)

in which Y represents a hydrogen or halogen atom or a C_{1-4} alkyl radical, Z represents a naphthyl radical or a radical



in which each of X_1 and X_2 independently of one another is a hydrogen or halogen atom, a C_{1-4} alkoxy radical, a C_{1-6} alkyl radical or CF_3, CH_3S, CH_3SO_2 or NO_2 and each of R_1 and R_2 independently of one another represents a hydrogen atom, a straight or branched C_{1-5} alkyl radical which is unsubstituted or substituted by one or more halogen atoms, hydroxyl, $N(C_{1-4}alkyl)_2$,

carbamoyl or C_{1-4} alkoxy radicals, an allyl radical, a propargyl radical, a C_{3-6} cycloalkyl radical, a benzyl radical or a phenyl radical, not both R_1 and R_2 being hydrogen, or NR_1R_2 represents a heterocyclic ring containing from 3 to 6 carbon atoms, or a heterocyclic ring of the formula,  R , in which X is O, S, CHOR' or $\geq$NR, R' being hydrogen or benzyl and R being hydrogen, a C_{1-4} alkyl radical or phenyl which is unsubstituted or substituted by methoxy or a halogen atom.

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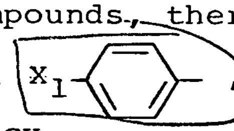
The preferred compounds of the invention are those in which R_1 and R_2 are both alkyl radicals. Amongst these compounds, those in which Y is in the 6-position and represents either a halogen atom or the methyl radical are particularly preferred. Finally, amongst the latter compounds, there may be mentioned those in which Z is a radical  R , in which X_1 is a halogen atom or the radical CH_3.

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According to a feature of the invention, the compounds of formula (I) can be prepared according to the following reaction scheme :

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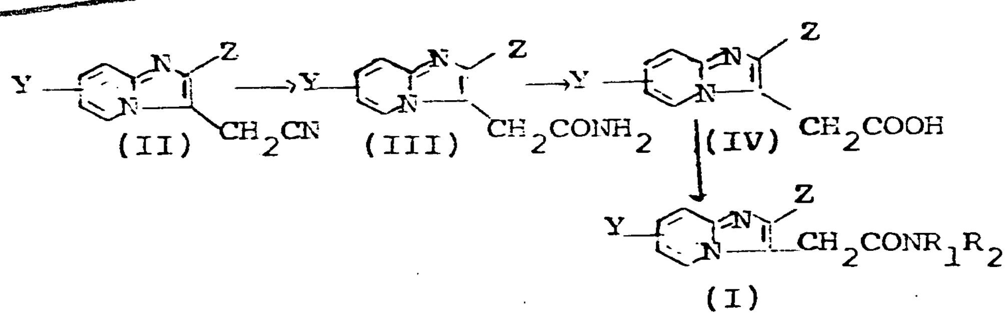


The reaction for the conversion of the nitrile (II) to the primary amide is carried out in accordance with a conventional method, for example with the aid of an acid such as dry hydrogen chloride, in a solvent such as formic acid, at a temperature from 15 to 50°C.

The saponification of the primary amide (III) to the acid (IV) may be carried out in ethanolic potassium hydroxide at the reflux temperature.

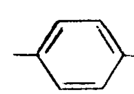
The conversion of the acid (IV) to the amide compound of formula (I) is carried out in accordance with any suitable method, for example by reacting the acid (IV) with the amine HNR_1R_2, in the presence of carbonyldiimidazole, or by reacting the chloride of the acid (IV) with the amine HNR_1R_2.

The general method for the preparation of the starting nitriles (II) is described in the literature, in particular in British Patent 1,076,089.

The following Examples illustrate the present invention. The analyses and the IR and NMR spectra confirm the structure of the compounds.

EXAMPLE 1

6-Chloro-2-(4-chlorophenyl)-imidazo[1,2-a]-pyridine-3-N, N-dimethylacetamide.

[Y = 6-Cl, Z = Cl, R_1 = R_2 = CH_3]

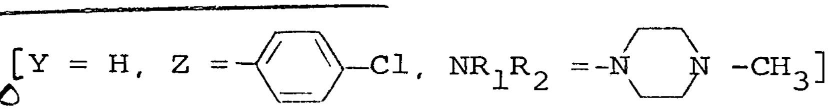
1. 22 g (0.0788 mol) of 6-chloro-2-(4-chlorophenyl)imidazo[1,2-a]pyridine-3-acetonitrile are added to 85 ml of 99% formic acid and the solution is treated with a stream of dry hydrogen chloride for 3 to 4 hours. When all the nitrile has been converted, the solution is heated slightly to degas it, and the cooled solution is then poured into 1 litre of water; the mixture is stirred for 10 minutes and then rendered alkaline with 200 ml of concentrated ammonia solution. The solid is filtered off, washed copiously with water and dried under a waterpump vacuum. The 6-chloro-2-(4-chlorophenyl)imidazo[1,2-a]pyridine-3-acetamide is recrystallised from ethanol. Melting point = 285-7°C

2. 19.2 g of 6-chloro-2-(4-chlorophenyl)-imidazo-[1,2-a]pyridine-3-acetamide and 19 g of KOH are added successively to 550 ml of 75% ethanol. The suspension is heated at the reflux temperature for 10-16 hours. When the reaction has ended, the solution is concentrated _in vacuo_ and the residue is dissolved in 1/2 litre of water. The small amount of insoluble material is filtered off and the filtrate is treated with 50 ml of acetic acid. The expected acid precipitates and it is filtered off and roughly dried. The crude product is taken up in 500 ml of acetone and the 6-chloro-2-(4-chlorophenyl)-imidazo[1,2-a]pyridine-3-acetic acid is filtered off hot. Melting point = 258-260°C

3. 4 g (12.45 millimols) of 6-chloro-2-(4-chlorophenyl)-imidazo[1,2-a]pyridine-3-acetic acid and 2.42 g (14.94 millimols) of carbonyldiimidazole are suspended in 60 ml of dry tetrahydrofuran. The reaction mixture is stirred at 20°C until the evolution of carbon dioxide has ended, and is then heated gently at 40°C for 15 minutes and cooled to 0°C. A solution of 14.94 millimols of dimethylamine in 5 ml of tetrahydrofuran is then added. The suspension is stirred for 15 minutes at 20°C and then concentrated; the residue is treated with 300 ml of water and 50 ml of a saturated aqueous solution of $NaHCO_3$. The insoluble material is filtered off, washed with water and dried. The compound obtained is recrystallised from a solvent such as ethanol. Melting point = 230°C

EXAMPLE 2

4-Methyl-1-{[2-(4-chlorophenyl)-imidazo[1,2-a]-pyridin-3-yl]-methylcarbonyl}-piperazine.



4.5 g (15.64 millimols) of 2-(4-chlorophenyl)-imidazo[1,2-a]pyridine-3-acetic acid are added to a suspension of N,N-dimethyl-chloro-methyleneiminium chloride prepared by adding 2.2 g (17.75 millimols) of oxalyl chloride to 30 ml of dimethylformamide (DMF) at -10°C.

The suspension is stirred for 15 minutes at 0°C and a solution of 5.4 g (54 millimols) of 4-methylpiperazine in 10 ml of dry DMF is then added gradually thereto at 0°C. The solution is stirred for 8 hours and then poured into 750 ml of water. The amide is extracted with CH_2Cl_2, the organic phase is dried over Na_2SO_4 and concentrated, the residue is passed through a silica column (eluant: CH_2Cl_2/CH_3OH 9/1) and the compound obtained is recrystallised from an isopropyl ether/acetonitrile mixture. Melting point = 175°C

The compounds listed in the following Table were similarly prepared.

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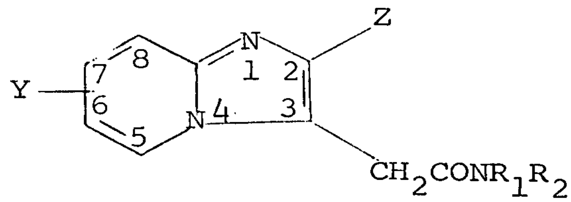
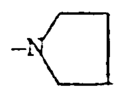
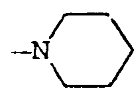
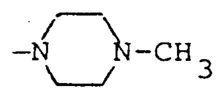
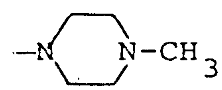
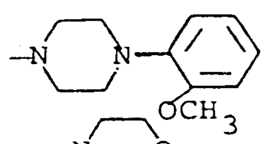
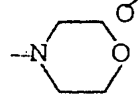
TABLE



Compound	Y	Z	NR_1R_2	Melting point (°C)
1	H	$4\text{-}Cl\text{-}C_6H_4$	$-NHCH_3$	234
2	H	$4\text{-}Cl\text{-}C_6H_4$	$-N(CH_3)_2$	179
3	H	$4\text{-}Cl\text{-}C_6H_4$		187-8
4	H	$4\text{-}Cl\text{-}C_6H_4$		190
5	H	$4\text{-}Cl\text{-}C_6H_4$		175
6	H	$3\text{-}CF_3\text{-}C_6H_4$		157.5-158
7	H	$4\text{-}Cl\text{-}C_6H_4$		206-7
8	H	$4\text{-}Cl\text{-}C_6H_4$		242
9	6-Cl	$4\text{-}Cl\text{-}C_6H_4$	$-NHCH_3$	>290
10	6-Cl	$4\text{-}Cl\text{-}C_6H_4$	$-NHC_2H_5$	280-2
11	6-Cl	$4\text{-}Cl\text{-}C_6H_4$	$-NH\text{-}n\text{-}C_3H_7$	229-30

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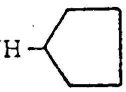
<u>TABLE</u> (continuation 1)

Compound	Y	Z	NR_1R_2	Melting point (°C)
12	6-Cl	4-Cl-C_6H_4	$-NH-i-C_3H_7$	259
13	6-Cl	4-Cl-C_6H_4	$-NH-n-C_4H_9$	225
14	6-Cl	4-Cl-C_6H_4	$-NH-t-C_4H_9$	224
15	6-Cl	4-Cl-C_6H_4	-NH- 	243-5
16	6-Cl	4-Cl-C_6H_4	$-NHC_6H_5$	265-7
17	6-Cl	4-Cl-C_6H_4	$-NHCH_2C_6H_5$	253-4
18	6-Cl	4-Cl-C_6H_4	$-NHCH_2CH_2OH$	260-1
19	6-Cl	4-Cl-C_6H_4	$-NHCH_2CH_2OCH_3$	197
20	6-Cl	4-Cl-C_6H_4	$-NHCH_2CH_2N(CH_3)_2$	199-201
21	6-Cl	4-Cl-C_6H_4	$-NHCH_2CH=CH_2$	233
22	6-Cl	4-Cl-C_6H_4	$-NHCH_2-C\equiv CH$	239
23	6-Cl	4-CH_3-C_6H_4	$-NHC_2H_5$	238
24	6-Cl	4-Cl-C_6H_4	$-NHCH_2CF_3$	258
25	6-Cl	4-Cl-C_6H_4	$-NHCH_2CONH_2$	256-7
26	6-Cl	4-Cl-C_6H_4	$-N(CH_3)_2$	230
27	6-Cl	4-Cl-C_6H_4	$-N(C_2H_5)_2$	149
28	6-Cl	4-Cl-C_6H_4	$-N(n-C_3H_7)_2$	140-1

<u>TABLE</u> (continuation 2)

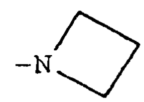
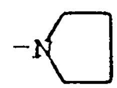
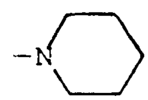
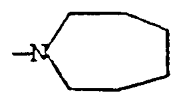
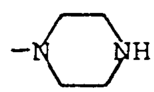
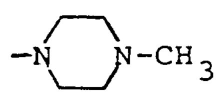
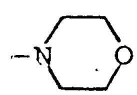
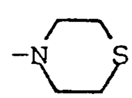
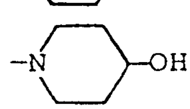
Compound	Y	Z	NR_1R_2	Melting point (°C)
29	6-Cl	$4\text{-Cl-}C_6H_4$	$-N(CH_3)(n\text{-}C_3H_7)$	160
30	6-Cl	$4\text{-Cl-}C_6H_4$	$-N(CH_3)(CH(CH_3)_2)$	185-6
31	6-Cl	$4\text{-Cl-}C_6H_4$	$-N(n\text{-}C_4H_9)_2$	149-150
32	6-Cl	$4\text{-Cl-}C_6H_4$		243-5
33	6-Cl	$4\text{-Cl-}C_6H_4$		219-220
34	6-Cl	$4\text{-Cl-}C_6H_4$		208-9
35	6-Cl	$4\text{-Cl-}C_6H_4$		190-2
36	6-Cl	$4\text{-Cl-}C_6H_4$	 . 2HCl	> 300
37	6-Cl	$4\text{-Cl-}C_6H_4$		204-6
38	6-Cl	$4\text{-Cl-}C_6H_4$		262
39	6-Cl	$4\text{-Cl-}C_6H_4$		239-241
40	6-Cl	$4\text{-Cl-}C_6H_4$		270
41	$6\text{-}CH_3$	$4\text{-Cl-}C_6H_4$	$-NHCH_3$	261-2
42	$6\text{-}CH_3$	$4\text{-Cl-}C_6H_4$	$-NHC_2H_5$	224-5

TABLE (continuation 3)

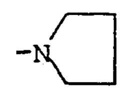
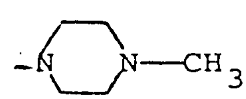
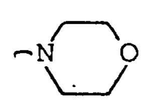
Compound	Y	Z	NR_1R_2	Melting point (°C)
43	6-CH_3	4-Cl-C_6H_4	-NH-CH_2CH_2OH	246
44	6-CH_3	4-Cl-C_6H_4	-N$(CH_3)_2$	215
45	6-CH_3	4-Cl-C_6H_4	-NH-CH_2-CH_2-Cl	202
46	6-CH_3	4-Cl-C_6H_4		194
47	6-Cl	C_6H_5	-NHCH_3	276-7
48	6-Cl	C_6H_5	-N$(CH_3)_2$	192
49	6-Cl	4-CH_3-C_6H_4	-NHCH_3	277-8
50	6-Cl	4-CH_3-C_6H_4	-N$(CH_3)_2$	185-6
51	6-Cl	4-CH_3O-C_6H_4	-NHCH_3	273
52	6-Cl	4-CH_3O-C_6H_4	-N$(CH_3)_2$	166
53	6-Cl	4-Br-C_6H_4	-NHC_2H_5	287
54	6-Cl	4-Br-C_6H_4	-N$(C_2H_5)_2$	168
55	6-Cl	naphth-2-yl		217-8
56	6-Cl	naphth-2-yl		193-4
57	6-Cl	naphth-1-yl	-N$(CH_3)_2$	187-8
58	6-Cl	2-CH_3-C_6H_4	-NHCH_3	175-6

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TABLE (continuation 4)

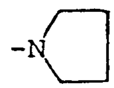
Compound	Y	Z	NR_1R_2	Melting point (°C)
59	6-Cl	$2\text{-}CH_3\text{-}C_6H_4$	$-NHC_2H_5$	161-2
60	6-Cl	$2\text{-}CH_3O\text{-}C_6H_4$	$-NHC_2H_5$	172-3
61	6-Cl	$3\text{-}Cl\text{-}C_6H_4$	$-NHC_2H_5$	215-6
62	6-Cl	$3\text{-}CH_3O\text{-}C_5H_4$	$-N(C_2H_5)_2$	98-9
63	6-Cl	$3\text{-}CH_3O\text{-}C_6H_4$		190
64	6-Cl	$3,4\text{-}Cl_2\text{-}C_6H_3$	$-N(CH_3)_2$	221-2
65	6-Cl	$3,4\text{-}(CH_3O)_2\text{-}C_6H_3$	$-N(CH_3)_2$	215
66	6-Cl	$3,4\text{-}(CH_3O)_2\text{-}C_6H_3$	$-N(n\text{-}C_3H_7)_2$	147
67	$7\text{-}CH_3$	$4\text{-}Cl\text{-}C_6H_4$	$-NHC_2H_5$	228
68	$7\text{-}CH_3$	$4\text{-}Cl\text{-}C_6H_4$	$-N(CH_3)_2$	206
69	$8\text{-}CH_3$	$4\text{-}Cl\text{-}C_6H_4$	$-NHCH_3$	234
70	$8\text{-}CH_3$	$4\text{-}Cl\text{-}C_6H_4$	$-N(C_2H_5)_2$	175,5
71	6-Cl	$4\text{-}F\text{-}C_6H_4$	$-N(CH_3)_2$	210
72	6-Cl	$4\text{-}F\text{-}C_6H_4$	$-N(n\text{-}C_4H_9)_2$	129
73	$6\text{-}CH_3$	$4\text{-}F\text{-}C_6H_4$	$-N(CH_3)_2$	195
74	6-Cl	$4\text{-}Br\text{-}C_6H_4$	$-N(CH_3)_2$	228-9

TABLE (continuation 5)

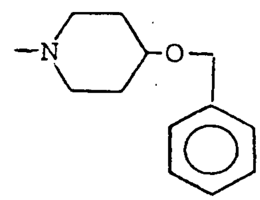
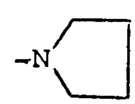
Compound	Y	Z	NR_1R_2	Melting point (°C)
75	6-CH_3	4-CH_3-C_6H_4	-$N(CH_3)_2$	196
76	6-CH_3	4-Cl-C_6H_4	-$N(n\text{-}C_4H_9)_2$	116
77	6-Cl	4-Cl-C_6H_4		152
78	H	4-Cl-C_6H_4	-$N(n\text{-}C_3H_7)_2$	136
79	H	4-Cl-C_6H_4	-$N(n\text{-}C_4H_9)_2$	105
80	6-Cl	4-Cl-C_6H_4	-$N(n\text{-}C_5H_{11})_2$	92-3
81	6-CH_3	4-CH_3-C_6H_4	-$NHCH_3$	187
82	6-CH_3	4-CH_3-C_6H_4	-NHC_2H_5	184
83	6-CH_3	4-$CH_3C_6H_4$	-$N\langle^{CH_3}_{nC_3H_7}$	108
84	6-CH_3	4-$CH_3C_6H_4$	-$N(n\text{-}C_3H_7)_2$	115
85	6-CH_3	4-CH_3-C_6H_4		168
86	6-CH_3	4-Cl-C_6H_4	-$NHCH_2CF_3$	239
87	6-CH_3	4-Br-C_6H_4	-NHC_2H_5	232-4
88	6-CH_3	4-Br-C_6H_4	-$N(CH_3)_2$	203.5-205

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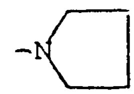
TABLE (continuation 6)

Compound	Y	Z	NR_1R_2	Melting point (°C)
89	6-CH_3	4-Br-C_6H_4	$-N(n-C_3H_7)_2$	138-9
90	6-CH_3	4-Br-C_6H_4		195,5-197
91	6-CH_3	4-CH_3O-C_6H_4	$-N(CH_3)_2 \cdot CH_3SO_3H$	230-2
92	6-CH_3	4-CH_3S-C_6H_4	$-N(CH_3)_2 \cdot CH_3SO_3H$	209
93	6-CH_3	4-CH_3SO_2-C_6H_4	$-N(CH_3)_2$	227-9
94	6-CH_3	4-NO_2-C_6H_4	$-NHC_2H_5$	268-270
95	6-CH_3	4-NO_2-C_6H_4	$-N(CH_3)_2$	262-3
96	6-CH_3	4-t-C_4H_9-C_6H_4	$-N(CH_3)_2$	199-200
97	6-Cl	4-Cl-C_6H_4	$-N(CH_3)(C_2H_5)$	173

The compounds of the invention were subjected to pharmacological experiments which showed their valuable pharmacological properties in various areas.

The toxicity of the compounds was determined on mice by intraperitoneal administration. The LD 50 ranges from 500 to 1,000 mg/kg.

P The anxiolytic activity was determined according to the eating test (R.J. Stephens, (1973), Brit. J. Pharmac., 49, 146 P). In this test, the doses which increase the food consumption of the mice vary from 0.1 to 10 mg/kg, administered intraperitoneally.

The activity of the compounds in the area of cerebral circulation was determined in the test for the hypoxia caused by pressure reduction. Mice of the CD1 strain are kept in an oxygen-depleted atmosphere produced by creating a partial vacuum (190 mm of mercury, corresponding to 5.25% of oxygen). The survival time of the animals is noted. This time is increased by agents which are capable of assisting the oxygenation of tissues and in particular of the brain. The compounds studied are administered intraperitoneally in several doses, 10 minutes before the experiment. The percentage increases in the survival time, relative to the values obtained for control animals, are calculated. The mean active dose (MAD), that is to say the dose which increases the survival time by 100%, is determined graphically. The MAD ranges from 0.3 to 32 mg/kg, administered intraperitoneally.

The anticonvulsant activity was determined in accordance with the test for the antagonism towards the mortality induced by bicuculline in mice (P. Worms, H. Depoortere and K.G. Lloyd, (1979) Life Sci., <u>25</u>,

607-614). The products to be studied are injected intraperitoneally, 30 minutes before the bicuculline (0.9 mg/kg, administered intravenously). With death being the criterion selected for this test, the percentage mortalities are noted for each batch, 2 hours after administration of the bicuculline (control batch: 100% mortality). For each product, the 50% active dose (AD 50 or the dose which protects 50% of the animals from the lethal effects of the bicuculline) is determined graphically. The AD 50 of the compounds of the invention vary between 0.3 and 30 mg/kg, administered intraperitoneally.

The sedative or hypnotic activity was determined by observing the action of the compounds on the EEG of curarised rats and also on the wake-sleep states in freely moving, implanted rats and cats (H. Depoortere, Rev. E.E.G. Neurophysiol., (1980) 10, 3, 207-214; L.M. Da Costa, H. Depoortere and R. Naquet, Rev. E.E.G. Neurophysiol., (1977), 7, 2, 158-164). In curarised rats, the products to be studied were injected intraperitoneally or orally at doses increasing from 0.1 to 30 mg/kg. They induce sleep traces starting from doses ranging from 0.1 to 10 mg/kg, administered intraperitoneally or orally. In freely moving, implanted rats, the products to be studied were injected intraperitoneally or orally at a single dose ranging

from 1 to 10 mg/kg. At these doses, they reduce the total wake time by 13 to 44%, without significantly changing the total paradoxical sleep time, certain products even increasing the total duration of this phase of sleep. In freely moving, implanted cats, the products to be studied were injected intraperitoneally or orally at a single dose of 10 mg/kg. They transitorily increase the wake time after injection, this being accompanied by benzodiazepine-type jactation, and reduce the total paradoxical sleep time by 40 to 100%. However, certain products increase the total duration of the SWSP (slow-wave sleep with phase phenomena: P.G.O. points) by about 50%.

The results of these various tests show that the compounds of the invention possess anxiolytic, anti-anoxic, sleep-inducing, hypnotic and anticonvulsant properties; the compounds of the invention are useful for the treatment of anxiety states, sleep disorders and other neurological and psychiatric complaints, for the treatment of vigilance disorders, in particular for combating behavioural disorders which can be attributed to cerebral vascular damage and to the cerebral sclerosis encountered in geriatrics, and also for the treatment of epileptic vigilance due to cranial traumatisms and for the treatment of metabolic encephalopathies.

The compounds of the invention can be presented in any form which is suitable for oral or parenteral administration, for example in the form of tablets, coated tablets, capsules, solutions to be taken orally or injected, and the like, with any suitable excipient. The daily posology can range from 0.5 to 2,000 mg.